

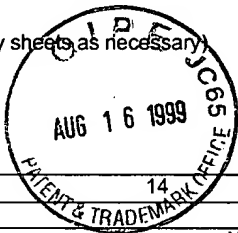
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> (use as many sheets as necessary)		Application Number	09/139,425
		Filing Date	August 25, 1998
		First Named Inventor	Charles T. Esmon
		Group Art Unit	<del>4642</del> 1636
		Examiner Name	W. Sandals
		Attorney Docket Number	OMRF 171
Sheet	1	of	14



U.S. PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	US Patent Document		Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code* (if known)			
JS		3,625,214		Higuchi	12-07-1971	424, 424
D		4,244,946		Rivier	01-13-1981	514, 15
JS		4,305,872		Johnston, et al.	12-15-1981	530, 330
JS		4,316,891		Guilleman, et al.	02-23-1982	514, 11
JS		4,629,784		Stammer	12-16-1986	530, 328
JS		4,789,734		Pierschbacher	12-06-1988	530, 395
JS		4,782,137		Hopp, et al.	11-01-1988	530, 328
JS		4,792,525		Ruoslahti, et al.	12-20-1988	438, 402
JS		4,906,474		Langer, et al.	03-06-1990	514, 772, 3
JS		4,925,673		Steiner, et al.	05-15-1990	424, 455
JS		4,980,286		Morgan, et al.	12-25-1990	435, 371
JS		5,009,889		Taylor, et al.	04-23-1991	424, 94, 64
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JS		5,749,968		Melanson, et al.	05-12-1998	118, 300
JS		5,779,673		Roth, et al.	07-14-1998	604, 101
JS		5,804,392		Esmon, et al.	09-08-1998	435, 7, 1

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		Office. <sup>3</sup>	Number <sup>2</sup>	Kind Code <sup>5</sup> (if known)				
JS		WO	96/05303		Okla. Med. Res. Found.	02-22-1996		
JS		WO	96/20732		Chiron Viagene	07-11-1996		
JS		WO	96/21470		Genemedicine, Inc.	07-18-1996		
JS		WO	98/20041		Okla. Med. Res. Found	05-14-1998		

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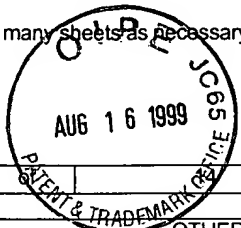
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		Group Art Unit	1643-1636
		Examiner Name	W. Sandals
		Attorney Docket Number	OMRF 171
Sheet	2		



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JS		ABE, et al., "Granulocyte proteases and hydrogen peroxide synergistically inactive thrombomodulin of endothelial cells in vitro," <i>J. Lab. Clin. Med.</i> 123(6):874-881, (1994).	
AS		ACCP/SCCM Consensus Conference, "Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis," <i>Chest</i> 101(6):1644-1655 (1992).	
AS		AGRAWAL, et al., "Oligodeoxynucleoside phosphoramidates and phosphorothioates as inhibitors of human immunodeficiency virus," <i>Proc. Natl. Acad. Sci. USA</i> 85(19):7079-7083 (1988).	
AS		AREND, et al., "Building of IL-1 $\alpha$ , IL-1 $\beta$ , and IL-1 Receptor Antagonist by Soluble IL-1 Receptors and Levels of Soluble IL-1 Receptors in Synovial Fluids," <i>J. Immunol.</i> 153:4766-4774 (1994).	
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AS		BANGALORE, et al., "High affinity binding sites for activated protein C and protein C on cultured human umbilical vein endothelial cells. Independent of protein S and distinct from known ligands," <i>Thromb Haemos</i> 72(3):465-74 (1994).	
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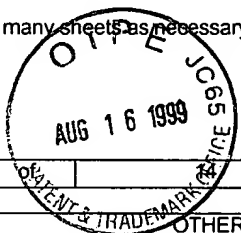
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		Group Art Unit	<del>4643</del> 1636
		Examiner Name	W. Sandals
Sheet	3	Attorney Docket Number	OMRF 171



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JS		BOEHME, et al., "Release of thrombomodulin from endothelial cells by concentrated action of TNF- $\alpha$ and neutrophils: <i>in vivo</i> and <i>in vitro</i> studies," <i>Immunology</i> 87:134-140 (1996).	
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JS		DAUGHERTY, et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting, and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," <i>Nucl. Acids Res.</i> 19(9):2471-2476 (1991).	
JS		DITTMAN and MAJERUS, "Structure and Function of Thrombomodulin: A Natural Anticoagulant," <i>Blood</i> 75(2):329-336 (1990).	

Examiner's Signature	William Sandals	Date Considered	10/14/98
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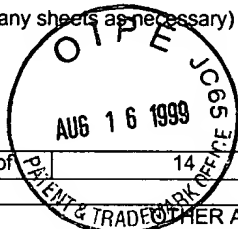
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Sheet	4	of	14



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h		DITTMAN, W. A. "Thrombomodulin - Biology and Potential Cardiovascular Applications," <i>Trends Cardiovasc. Med.</i> 1(8):331-336 (1991).	
m		DREYFUS et al., "Treatment of Homozygous Protein C Deficiency and Neonatal Purpura Fulminans with a Purified Protein C Concentrate," <i>N. Engl. J. Med.</i> 325(22):1565-1568 (1991).	
m		DUVAL-VALENTIN, ET AL., "Specific inhibition of transcription by triple helix-forming oligonucleotides," <i>Proc Natl Acad Sci U S A.</i> 89(2):504-8 (1992).	
m		ECKE, et al., "Possible identity of kallikrein binding protein with protein C inhibitor," <i>Agents Actions Suppl.</i> 38 ( Pt 1):182-9 (1992).	
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m		ENGELMAN et al., "Identifying Nonpolar Transbilayer Helices in Amino Acid Sequences of Membrane Proteins," <i>Annu. Rev. Biophys. Chem.</i> 15:321-53 (1986).	
m		ESMON and OWEN, "Identification of an endothelial cell cofactor for thrombin-catalyzed activation of protein C," <i>Proc. Natl. Acad. Sci. (USA)</i> 78(4):2249-2252 (1981).	
m		ESMON and SCHWARZ, "An Update on Clinical and Basic Aspects of the Protein C Anticoagulant Pathway," <i>Trends Cardiovasc. Med.</i> 5(4):141-148 (1995).	
m		ESMON, "Factors regulating the inhibition of thrombin by antithrombin III," in <i>Chemistry and Biology of Thrombin</i> , R. L. Lundblad, J. W. Fenton, II, and K. G. Mann, editors. Ann Arbor Science, Ann Arbor., 403-411 (1977).	
m		ESMON, "Protein S and Protein C - Biochemistry, Physiology, and Clinical Manifestation of Deficiencies," <i>Trends Cardiovasc. Med.</i> 2(6):214-220 (1992).	

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by		ESMON, "The Roles of Protein C and Thrombomodulin in the Regulation of Blood Coagulation," <i>J. Biol. Chem.</i> 264(9):4743-4746 (1989).	
12		ESMON, et al., "Complex Formation Between Thrombin Thrombomodulin Inhibits Both Thrombin-catalyzed Fibrin Formation and Factor V Activation," <i>J. Biol. Chem.</i> 257(14):7944-7947 (1982).	
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17		FUKUDOME and ESMON, "Identification, Cloning, and Regulation of a Novel Endothelial Cell Protein C/Activated Protein C Receptor," <i>J. Biol. Chem.</i> 269(42):26486-26491 (1994).	
17		FUKUDOME and ESMON, "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell Protein C/Activated Protein C Receptor (EPCR) - The Structural and Functional Conservation in Human, Bovine and Murine EPCR*," <i>J. Biol. Chem.</i> 270(10):5571-5577 (1995).	
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17		GRAHAM, et al., "A new technique for the assay of infectivity of human adenovirus 5 DNA.," <i>Virology.</i> 52(2):456-67 (1973).	
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AS		GREY, et al., "Selective effects of protein C on activation of human monocytes by lipopolysaccharide, interferon-gamma, or PMA: modulation of effects on CD11b and CD14 but not CD25 or CD54 induction," <i>Transplant Proc.</i> 25(5):2913-4 (1993).	
AN		GRIGORIEV, et al., "A triple helix-forming oligonucleotide-intercalator conjugate acts as a transcriptional repressor via inhibition of NF kappa B binding to interleukin-2 receptor alpha-regulatory sequence," <i>J Biol Chem</i> 267(5):3389-95 (1992).	
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AN		HEANEY, et al., "Membrane-associated and soluble granulocyte/macrophage-colony -stimulating factor receptor $\alpha$ subunits are independently regulated in HL-60 cells," <i>Proc. Natl. Acad. Sci. U.S.A.</i> 92:2365-2369 (1995).	
AN		HEANEY, ML and DW Golde, "Soluble cytokine receptors," <i>Blood</i> 87(3):847-857 (1996).	
AN		HOFSTEENGE, et al., "Effect of thrombomodulin on the kinetics of the interaction of thrombin with substrates and inhibitors," <i>Biochem. J.</i> 237:243-251 (1986).	
AN		HOGG, et al., "Identification of structural domains in protein C involved in its interaction with thrombin-thrombomodulin on the surface of endothelial cells," <i>J Biol Chem</i> 267(2):703-6 (1992).	
AN		HOLT, ET AL., "An oligomer complementary to c-myc mRNA inhibits proliferation of HL-60 promyelocytic cells and induces differentiation," <i>Mol Cell Biol.</i> 8(2):963-73 (1988).	
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AN		ISHII and MAJERUS, "Thrombomodulin is Present in Human Plasma and Urine," <i>J. Clin. Invest.</i> 76:2178-2181 (1985).	

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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Application Number	09/139,425
		Filing Date	August 25, 1998
		First Named Inventor	Charles T. Esmon
		Group Art Unit	1643-1636
		Examiner Name	W. Sandals
Sheet 7 of 14		Attorney Docket Number	OMRF 171

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W		ITAKURA, et al., "Synthesis and Use of Synthetic Oligonucleotides," in <i>Ann. Rev. Biochem.</i> 53:323-356 (1984).	
W		JACKMAN, et al., "Human thrombomodulin gene is intron depleted: Nucleic acid sequences of the cDNA and gene predict protein structure and suggest sites of regulatory control," <i>Proc. Natl. Acad. Sci. (USA)</i> 84:6425-6429 (1987).	
W		JIANG, et al., "Nucleocytoplasmic transport is enhanced concomitant with nuclear accumulation of epidermal growth factor (EGF) binding activity in both 3T3-1 and EGF receptor reconstituted NR-6 fibroblasts," <i>J. Cell Biol.</i> 110:559-568 (1990).	
W		KABAT, et al., <i>Sequences of Proteins of Immunological Interest</i> , 4th Ed. (U.S. Dept. Health and Human Services, Bethesda, MD, 1987)	
W		KAISHO, et al., "BST-1, a surface molecule of bone marrow stromal cell lines that facilitates pre-B-cell growth.," <i>Proc Natl Acad Sci U S A.</i> 91(12):5325-9 (1994).	
W		KAPIOTIS, et al., "Interleukin-4 counteracts pyrogen-induced downregulation of thrombomodulin in cultured human vascular endothelial cells," <i>Blood.</i> 78(2):410-5 (1991).	
W		KOZAK, et al., "Point mutations define a sequence flanking the AUG initiator codon that modulates translation by eukaryotic ribosomes," <i>Cell</i> 44(2):283-92 (1986).	
W		KUROSAWA, et al., "Identification of functional Endothelial Protein C Receptor in Human Plasma," <i>J. Clin. Invest.</i> 100(2): 411-418 (1997).	
W		KYTE, et al., "A simple method for displaying the hydropathic character of a protein," <i>J Mol Biol</i> 157(1):105-32 (1982).	
W		LAEMMLI, "Cleavage of Structural Proteins During the Assembly of the Head of Bacteriophage T4," <i>Nature</i> , 227:680-685 (1970).	

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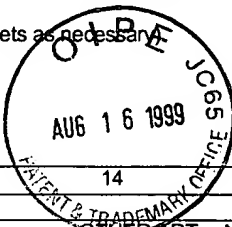
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JS		LASZIK, et al., "The Human Protein C Receptor Is Present Primarily on Endothelium of Large Blood Vessels," <i>Circulation</i> , 96(10):1-9 (1997).	
JS		LE BONNIEC, ET AL., "The role of calcium ions in factor X activation by thrombin E192Q," <i>J Biol Chem</i> 267(10):6970-6 (1992).	
JS		LEDBETTER, ET AL., "Covalent association between human thymus leukemia-like antigens and CD8(Tp32) molecules," <i>J Immunol</i> 134(6):4250-4 (1985).	
JS		LENTZ et al., "Regulation of Thrombomodulin by Tumor Necrosis Factor-α: Comparison of Transcriptional and Posttranscriptional Mechanisms," <i>Blood</i> 77(3):543-550, (1991).	
JS		LEWIS, et al., "Automated site-directed drug design: the concept of spacer skeletons for primary structure generation," <i>Proc. R. Soc. Lond.</i> , 236(1283):125-140 (1989)	
JS		LEWIS, et al., "Automated site-directed drug design: the formation of molecular templates in primary structure generation," <i>Proc. R. Soc. Lond.</i> , 236(1283):141-162 (1989)	
JS		LOBIE, et al. "Nuclear translocation and anchorage of the growth hormone receptor," <i>J. Biol. Chem.</i> 269:31735-31746 (1994).	
JS		LU, et al., "The Active Site of the Thrombin-Thrombomodulin Complex - A Fluorescence Energy Transfer Measurement of its Distance Above the Membrane Surface*," <i>J. Biol. Chem.</i> 264(22):12956-12962 (1989).	
JS		LUST, et al., "Isolation of An mRNA Encoding a Soluble Form of the Human Interleukin-6 Receptor," <i>Cytokine</i> 4(2):96-100 (1992).	
JS		MACIAG, et al., "An endothelial cell growth factor from bovine hypothalamus: identification and partial characterization," <i>Proc Natl Acad Sci U S A.</i> 76(11):5674-8 (1979).	

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W		MAHER, "Nuclear Translocation of fibroblast growth factor (FGF) receptors in response to FGF-2," <i>J. Cell Biol.</i> 134:529-536 (1996).	
W		MAHER, ET AL., "Inhibition of DNA binding proteins by oligonucleotide-directed triple helix formation.,," <i>Science</i> 245(4919):725-30 (1989).	
W		MARUYAMA, et al., "Increased expression of thrombomodulin on the cultured human umbilical vein endothelial cells and mouse hemangioma cells by cyclic AMP," <i>Thromb Res.</i> 61(3):301-10 (1991).	
W		MATHER, et al., "The 2.8 Å Crystal Structure of Gla-Domainless Activated Protein C," <i>EMBO J.</i> 15(24):6822-6831 (1996).	
W		MATHEWS, "Structure of a Nonadecapeptide of the Fifth EGF Domain of Thrombomodulin Complexed with Thrombin," <i>Biochemistry</i> 33:13547-13552 (1994).	
W		MCKINLAY, et al., "Rational Design of Antiviral Agents," <i>Annual Review of Pharmacology and Toxicology</i> , 29:111-122 (1989)	
W		MERRIFIELD, "Solid-Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide," <i>J. Am. Chem. Soc.</i> 85:2149-2154 (1964).	
W		MIZUSHIMA, et al., "pEF-BOS, a powerful mammalian expression vector," <i>Nucleic Acids Res.</i> 18(17):5322 (1990).	
W		MOORE, et al., "Tumor Necrosis Factor Leads to the Internalization and Degradation of Thrombosis from the Surface of Bovine Aortic Endothelial Cells in Culture," <i>Blood</i> 73(1):159-165 (1989).	
W		MÜLLBERG, et al., "The Soluble Human IL-6 Receptor," <i>J. Immunol.</i> 152:4958-4968 (1994).	

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SN		MULLIGAN, et al., "The basic science of gene therapy," <i>Science</i> 260(5110):926-32 (1993)	
D		NARANG, et al., "Chemical Synthesis of Deoxyoligonucleotides by the Modified Triester Method," in <i>Methods Enzymol.</i> 65:610-620 (1980).	
N		NAWROTH, et al., "Modulation of endothelial cell hemostatic properties by tumor necrosis factor," <i>J Exp Med.</i> 163(3):740-5 (1986).	
SN		OFFENSBERGER, et al., "In Vivo inhibition of duck hepatitis B virus replication and gene expression by phosphorothioate modified antisense oligodeoxynucleotides," <i>EMBO J.</i> 12(3):1257-1262 (1993).	
SN		OHDAMA, et al., "Plasma Thrombomodulin in Wegener's Granulomatosis as an Indicator of Vascular Injuries," <i>Chest</i> 106:666-671 (1994).	
SN		OLSEN, ET AL., "Ca <sup>2+</sup> dependence of the interactions between protein C, thrombin, and the elastase fragment of thrombomodulin. Analysis by ultracentrifugation," <i>Biochemistry</i> 31(3):746-54 (1992).	
N		ORSON, ET AL., "Oligonucleotide inhibition of IL2R alpha mRNA transcription by promoter region collinear triplex formation in lymphocytes," <i>Nucleic Acids Res</i> 19(12):3435-41 (1991).	
SN		OWEN, et al., "The Conversion of Prothrombin to Thrombin," <i>J. Biol. Chem.</i> 249(2):594-605 (1974).	
N		PANJA, ET AL., "CD1d is involved in T cell-intestinal epithelial cell interactions," <i>J Exp Med.</i> 178(3):1115-9 (1993).	
N		PARKINSON, et al., "Stable Expression of a Secretable Deletion Mutant of Recombinant Human Thrombomodulin in Mammalian Cells," <i>J. Biol. Chem.</i> 265(21):12602-12610 (1990).	

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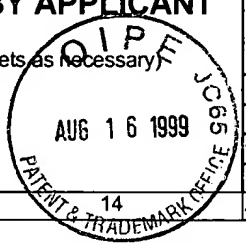


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PD		PERRY & DAVIES, <u>QSAR: Quantitative Structure-Activity Relationships in Drug Design</u> pp. 189-193 (Alan R. Liss, inc. 1989)	
PD		PORCELLI, ET AL., "CD1b restricts the response of human CD4-8- T lymphocytes to a microbial antigen," <i>Nature</i> , 360(6404):593-7 (1992).	
PD		POSTEL, et al., "Evidence that a triplex-forming oligodeoxyribonucleotide binds to the c-myc promoter in HeLa cells, thereby reducing c-myc mRNA levels," <i>Proc Natl Acad Sci U S A</i> . 88(18):8227-31 (1991).	
PD		PROUDFOOT, et al., "3' non-coding region sequences in eukaryotic messenger RNA," <i>Nature</i> 263(5574):211-4 (1976).	
PD		QUEHENBERGER, et al., "Increased Levels of Activated Factor VII and Decreased Plasma Protein S Activity and Circulating Thrombomodulin During Use of Oral Contraceptives," <i>Thromb. Haemost.</i> 76:729-734 (1996).	
PD		REGAN, et al., "The endothelial cell protein C receptor. Inhibition of activated protein C anticoagulant function without modulation of reaction with proteinase inhibitors," <i>J. Biol. Chem.</i> 271, 17499-17503 (1996).	
PD		REITSMA, et al., "Protein C Deficiency: A Database of Mutations, 1995 Update," <i>Thromb. Haemost.</i> 73:876-879 (1995).	
PD		REZAI, et al., "Communication: Protein C Inhibitor Is a Potent Inhibitor of the Thrombin-Thrombomodulin Complex," <i>J. Biol. Chem.</i> 270(43):25336-25339 (1995).	
PD		RIPKA, "Computers Picture the Perfect Drug," <i>New Scientist</i> , 54-57 (June 16, 1988)	
PD		ROLLINS, et al., "Inhibition of Homologous Complement by CD59 is Mediated by a Species-Selective Recognition Conferred Through Binding to C8 Within C5b-8 or C9 Within C5b-9," <i>J. Immunol.</i> 146(7):2345-2351 (1991).	

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		ROUVINEN, et al., "Computer-Aided Drug Design," <i>Acta Pharmaceutica Fennica</i> , 97:159-166 (1988)	
		SADLER, et al., "Structure-Function Relationships of the Thrombin-Thrombomodulin Interaction," <i>Haemostasis</i> 23(suppl 1):183-193 (1993).	
		SARIN, et al., "Inhibition of acquired immunodeficiency syndrome virus by oligodeoxynucleoside methylphosphonates," <i>Proc. Natl. Acad. Sci. USA</i> 85(20):7448-7794 (1989).	
		SEBESTYÉN, et al., "DNA vector chemistry: the covalent attachment of signal peptides to plasmid DNA," <i>Nature Biotechnology</i> 16, 80-85 (1998).	
		SELIGSOHN et al., "Homozygous Protein C Deficiency Manifested by Massive Venous Thrombosis in the Newborn," <i>N. Engl. J. Med.</i> 310(9):559-562 (1984).	
		SHAW, et al., "Modified deoxyoligonucleotides stable to exonuclease degradation in serum," <i>Nucleic Acids Res.</i> 19(4):747-750 (1991).	
		STEARNS, et al., "The Interaction of a Ca <sup>2+</sup> -dependent Monoclonal Antibody with the Protein C Activation Peptide Region," <i>J. Biol. Chem.</i> 263(2):826-832 (1988).	
		STEARNS-KUROSAWA, et al., "The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex," <i>Proc. Natl. Acad. Sci. (USA)</i> 93:10212-10216 (1996).	
		STERN, et al., "Cultured bovine aortic endothelial cells promote activated protein C-protein S-mediated inactivation of factor Va," <i>J Biol Chem</i> 261(2):713-8 (1986).	

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JS		SZOSTAK, "In Vitro genetics," <i>TIBS</i> 19:89-93 (1992).	
JS		TAKAHASHI, et al., "Circulating Thrombomodulin As a Novel Endothelial Cell Marker: Comparison of Its Behavior with von Willebrand Factor and Tissue Type Plasminogen Activator," <i>Am. J. Hematol.</i> 41:32-39 (1992).	
JS		TAKAHASHI, et al., "Circulating Thrombomodulin in Thrombotic Thrombocytopenic Purpura," <i>Am. J. Hematol.</i> 38:174-177 (1991).	
JS		TAKANO, et al., "Plasma Thrombomodulin in Health and Diseases," <i>Blood.</i> 76(10):2024-2029 (1990).	
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JS		TAYLOR et al., "C4b-Binding Protein Exacerbates the Host Response to <i>Escherichia coli</i> ," <i>Blood</i> 78(2):357-363 (1991).	
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Application Number	09/139,425
		Filing Date	August 25, 1998
		First Named Inventor	Charles T. Esmon
		Group Art Unit	1643-1636
		Examiner Name	W. Sandals
		Attorney Docket Number	OMRF 171
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Examiner's Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, cit and/or country where published	T <sup>2</sup>
W		WEN, et al., "Human Thrombomodulin: Complete cDNA Sequence and Chromosome Localization of the Gene," <i>Biochemistry</i> 26:4350-4357 (1987).	
D		WICKSTROM, et al., "Human promyelocytic leukemia HL-60 cell proliferation and c-myc protein expression are inhibited by an antisense pentadecadeoxynucleotide targeted against c-myc mRNA," <i>Proc Natl Acad Sci U S A.</i> 85(4):1028-32 (1988).	
W		WILLIAMS, ET AL., The immunoglobulin superfamily--domains for cell surface recognition., <i>Annu Rev Immunol</i> 6:381-405 (1988).	
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D		YE, et al., "The Fifth and Sixth Growth Factor-like Domains of Thrombomodulin Bind to the Anion-binding Exosite of Thrombin and Alter Its Specificity," <i>J. Biol. Chem.</i> 267(16):11023-11028 (1992).	
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D		ZHU, et al., "Systemic gene expression after intravenous DNA delivery into adult mice," <i>Science</i> 261(5118):209-11 (1993).	

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